Supplemental Data

The following section provides further information to help the reader better understand the molecular modeling processes and the conclusions that were drawn from it.

An initial set of sixteen PCBs was used to model SXR antagonism. Using PCB28 (K_i= 9.143 μM) as a gauge, the PCBs were divided into two categories in terms of antagonist activity: those with $K_i \leq 9$ μM and those with $K_i \geq 9$ μM. As described in the main text, the more active antagonistic PCBs tend to be more highly ortho-substituted. Accordingly, the antagonist activity was strong for PCBs 184 and 183 (4 and 3 ortho-Cl atoms, respectively) but was undetectable for PCBs 118 (1 ortho-Cl atom) and 169 (zero ortho-Cl atoms). A notable exception to this trend was decachlorobiphenyl (PCB209) that seemed to lack antagonist activity despite the presence of 4 ortho-Cl atoms. However, PCB209 also exhibited weak agonistic effects in our assays that could obscure detection of its antagonistic effects (Fig. 1).

Beyond this "ortho" effect, a more general substitution pattern began to emerge. Of the original set of sixteen PCBs tested, the six active antagonists display the following patterns: "square" (PCB184), "square-triangle" (PCB183), "triangle-triangle" (PCB153), "square" (PCB196), "triangle" (PCB187), and "triangle" (PCB180). (displayed in Supplemental Data Fig. 1).

PCBs 74, 99, 118, and 138 illustrate various subtle features that distinguish inactive and active antagonists of human SXR. All four of these PCBs contain the "triangle" substitution pattern on one ring, yet all are non-antagonists. It should be

pointed out that none of these inactive PCBs contain the more active "square" substitution pattern. However, examination of each compound as a whole provides more clues to their lack of antagonist activity. These compounds are generally deficient in terms of total number of Cl atoms and, in particular, ortho-substitution. PCBs 118 and 74 (Supplemental Data Fig. 1) are both obvious examples of this phenomenon. Furthermore, it appears that a PCB with one triangle pattern requires a minimum of three ortho substituents to be active. From this analysis, we can postulate that the presence of the distinctive triangle or square pattern is necessary but not sufficient for antagonist activity.

Supplemental Data Figure 1. PCBs that antagonize human SXR activation have distinctive substitution patterns.

Substitution patterns corresponding to 2,3,4,6 are shown as squares and 2,4,5 are shown as triangles imposed upon the PCBs used in this study. Note that the PCBs exhibiting the greatest antagonist activity contain a "square-square" (PCB197), "square-triangle" (PCB183), or "triangle-triangle" (PCB153) chlorine substitution pattern.

Second set of ten PCBs predicted by our computer models to possess significant antagonist activity for human SXR are indicated by a star (*) preceding the IUPAC number. Horizontal line separates the active versus inactive antagonists of human SXR.

Molecular modeling of PCBs was conducted on a Silicon Graphics Octane workstation using Sybyl 6.8 (Tripos, Inc., St. Louis, MO) for initial construction and Spartan'02 (Wavefunction, Inc, Irvine, CA) for conformational analysis. The conformational-energy profile of each PCB was explored using the AM1 semi-empirical molecular orbital method by rotating the central bond between the two rings in 10° increments to identify the low-energy conformer(s).

Supplemental Data Figure 1.